

### REMARKS

#### Rejection of claims under 35 U.S.C. 102:

Claims 1, 2, 4-6, 12-14, 16-18, and 20 are rejected under §102(a) as being anticipated by Isner *et al.* Applicants have amended the claims to obviate the rejection.

The terminology "lumen" and "hydrostatic pressure" has been added to further clarify the claims. Support for the language can be found in the Specification on page 16, line 2 and page 30, line 28.

Applicants claims now specify delivery by hydrostatic pressure into a blood vessel and then to cells outside of the blood vessel. In contrast, Isner *et al.* describes a balloon catheter coated with the compound to be delivered to endothelial cells.

Claims 1, 2, 4-6, 12-14, 16-18, and 20 are rejected under §102(e) as being anticipated by Mann *et al.*

The Mann *et al.* reference describes processes to deliver nucleic acid to endothelial cells. As discussed previously it is important to note that the Mann *et al.* invasive processes use pressure applied to the targeted cell.

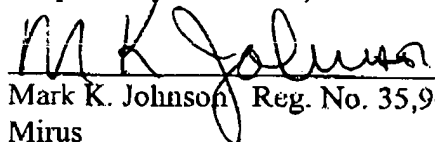
In contrast, Applicants use the living tissue wall of the blood vessel as the pressurized enclosure and the invasiveness is limited. The claims have been amended to further clarify Applicants' process.

On page 6, the Action rejects claims 1, 2, 4-6, 12-14, 16-18, and 20 as being anticipated by the Wolff *et al.*

Applicants have amended claims 1 and 18 to clarify that their process is directed to injecting the nucleic acid into a blood vessel and increasing hydrostatic pressure in the lumen. Conversely, the Wolff *et al.* patent does not teach, suggest or contemplate using hydrostatic pressure to deliver the nucleic acid into extravascular cells.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendments and discussion, it is submitted that claims 1, 2, 4-6, 12-14, 16-18, and 20 should be allowable and Applicants respectfully request an early notice to such effect.

Respectfully submitted,



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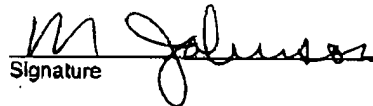
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Applicants hereby submit a version with markings to show changes made:

1. (Amended) [A process for delivering a nucleic acid to heart muscle cells in a mammal, comprising:

- a) injecting the nucleic acid into a heart blood vessel with pressure against blood vessel walls;
- b) delivering the nucleic acid out of the blood vessel to the heart muscle cells.]

A process for delivering nucleic acids to muscle cells in a mammalian heart, comprising: a) accessing an *in vivo* blood vessel; b) inserting an injector into the blood vessel near or in the heart, *in vivo*; c) injecting a solution containing nucleic acids into the blood vessel lumen and increasing hydrostatic pressure in the lumen; and, d) delivering the nucleic acids to the heart muscle cells outside of the blood vessel via the pressure, wherein invasiveness is limited to accessing the blood vessel, inserting the injector into the blood vessel, and injecting the solution.

18. (Amended) [A process for gene expression providing a therapeutic protein, comprising:

- a) injecting a nucleic acid into a heart blood vessel having a channel leading to heart muscle wherein injection pressure is applied to blood vessel walls;
- b) delivering the nucleic acid out of the blood vessel to a heart muscle cell; and,
- c) expressing the nucleic acid to provide a therapeutic protein.]

A process for gene expression in mammalian heart muscle cells, comprising: a) accessing an *in vivo* blood vessel; b) inserting an injector into the blood vessel near or in the heart, *in vivo*; c) injecting a solution containing nucleic acids encoding a protein into the blood vessel lumen and increasing hydrostatic pressure in the lumen; d) delivering the nucleic acids to the heart muscle cells outside of the blood vessel via the pressure; and, e) expressing the nucleic acids to provide a therapeutic protein, wherein invasiveness is limited to accessing the blood vessel, inserting the injector into the blood vessel, and injecting the solution.

Applicants hereby submit a version with markings to show changes made:

1) (Amended) [A process for delivering a nucleic acid to heart muscle cells in a mammal, comprising:

- a) introducing the nucleic acid to a heart vessel having a channel leading to heart muscle cells wherein there is not more than one heart vessel occlusion site per introduction;
- b) delivering the nucleic acid to the heart muscle cells.]

A process for delivering a nucleic acid to heart muscle cells in a mammal, comprising:

a) injecting the nucleic acid into a heart blood vessel with pressure against blood vessel walls;

b) delivering the nucleic acid out of the blood vessel to the heart muscle cells.

4) (Amended) The process of claim [3]\_2 wherein injecting the nucleic acid includes injecting the nucleic acid through a catheter.

18) (Amended) [A process for gene expression providing a therapeutic protein, comprising:

- a) inserting a nucleic acid into a blood vessel having a channel leading to heart muscle;
- b) delivering the nucleic acid to a heart muscle cell; and,
- c) expressing the nucleic acid to provide a therapeutic protein.]

A process for gene expression providing a therapeutic protein, comprising:

- a) injecting a nucleic acid into a heart blood vessel having a channel leading to heart muscle wherein injection pressure is applied to blood vessel walls;
- b) delivering the nucleic acid out of the blood vessel to a heart muscle cell; and,
- c) expressing the nucleic acid to provide a therapeutic protein.

20) (Amended) The process of claim [19]\_18 wherein injecting the nucleic acid includes injecting the nucleic acid through a catheter.

**We Claim:**

1) A process for delivering a nucleic acid to heart muscle cells in a mammal, comprising:

- Sub A1
- a) introducing the nucleic acid to a heart vessel having a channel leading to heart muscle cells wherein there is not more than one heart vessel occlusion site per introduction;
- b) delivering the nucleic acid to the heart muscle cells.

2) The process of claim 1 wherein the nucleic acid is expressed.

Sub A2

3) (Amended) The process of claim 2 wherein introducing [inserting] the nucleic acid comprises injecting the nucleic acid.

4) The process of claim 3 wherein injecting the nucleic acid includes injecting the nucleic acid through a catheter.

5) (Amended) [The process of claim 4 wherein delivering the nucleic acid includes increasing the blood vessel permeability.]

Sub A3

The process of claim 4 wherein delivering the nucleic acid includes increasing the heart vessel permeability.

6) (Amended) [The process of claim 5 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, and nucleic acid contained in viruses.]

The process of claim 5 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, oligonucleotides, and nucleic acid contained in viruses.

8) (Amended) The process of claim 7 wherein introducing [inserting] the nucleic acid comprises injecting the nucleic acid.

8) ~~The process of claim 7 wherein introducing the nucleic acid comprises injecting the nucleic acid.~~

9) ~~The process of claim 8 wherein injecting the nucleic acid includes injecting the nucleic acid through a catheter.~~

Sub A4

10) ~~The process of claim 9 wherein delivering the nucleic acid includes increasing the vessel permeability.~~

10) The process of claim 10 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, oligonucleotides, and viruses.

11) (Amended) The process of claim 9 wherein delivering the nucleic acid includes increasing the blood vessel permeability.

11) (Amended) The process of claim 10 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, oligonucleotides, and nucleic acid contained in viruses.

12) (Amended) The process of claim 4 wherein [delivering] injecting the nucleic acid includes [changing] injecting a predetermined volume of nucleic acid during a predetermined time.

13) The process of claim 12 wherein delivering the nucleic acid includes increasing the heart <sup>5</sup>  
the vessel permeability.

14) (Amended) The process of claim 13 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, and nucleic acid contained in viruses.

15) The process of claim 4 wherein delivering the nucleic acid includes increasing internal  
incr pressure of the heart vessel.

16) The process of claim 15 wherein delivering the nucleic acid includes increasing the heart  
the! vessel permeability.

17) (Amended) The process of claim 16 wherein the nucleic acid is selected from the group consisting of DNA, RNA, plasmid DNA, and nucleic acid contained in viruses.

18) A process for gene expression providing a therapeutic protein, comprising:

- a) inserting a nucleic acid into a blood vessel having a channel leading to heart muscle;
- b) delivering the nucleic acid to a heart muscle cell; and,
- c) expressing the nucleic acid to provide a therapeutic protein.

- b) delivering the nucleic acid to a cardiac tissue cell; and,
- c) expressing the nucleic acid.

19) The process of claim 18 wherein inserting the nucleic acid comprises injecting the nucleic acid.

20) The process of claim 19 wherein injecting the nucleic acid includes injecting the nucleic acid through a catheter.

#### New Claims:

21) The process of claim 1 wherein the nucleic acid consists of naked DNA.

22) The process of claim 18 wherein the nucleic acid consists of naked DNA.